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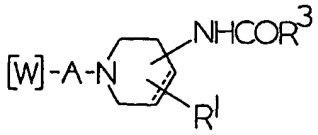
(54) OXIME DERIVATIVES

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, SL6 0PH, a British Company, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmacologically active piperidine derivatives, to processes for preparing them, and to pharmaceutical compositions containing them.

Piperidine derivatives having pharmacological activity are disclosed in U.K. Patent Specification No. 1,345,872 having the formula



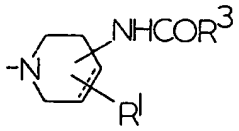
I(a)

in which the dotted line represents an optional double bond; W represents a cycloalkyl radical containing five to seven ring carbon atoms or an aryl or heteroaryl radical other than an indolyl radical, all of which radicals may be substituted or unsubstituted; A represents a lower alkylene radical, a mono- or di-keto lower-alkylene radical or an oxime, aminoguanidone or substituted or unsubstituted hydrazone derivative thereof, a hydroxy-lower-alkylene radical, or a bivalent radical of the formula

$$-NH-CO-(CH_2)_n-, \quad -N(\text{Acyl})-CH_2 . C\equiv C . CH_2-,$$

$$-O-CH_2\underset{\displaystyle OH}{CH} . CH_2- \quad \text{or} \quad -O-(\text{lower-alkylene})-,$$

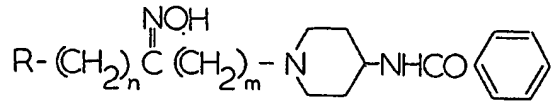
R^1 represents hydrogen, halogen or lower alkyl; R^3 represents a substituted or unsubstituted aryl radical (including heteroaryl radicals), aryl-lower alkyl, diaryl-lower alkyl, cycloalkyl containing from five to seven ring carbon atoms, lower alkoxy or lower alkyl radical; n is the integer 1, 2 or 3; Acyl is an acyl radical; and the term "lower" means the radical contains from 1 to 6 carbon atoms; and the acid addition and quaternary ammonium salts thereof; with the provisos that (i) when W is unsubstituted phenyl, and A is lower alkylene, and R^1 is lower alkyl, and R^3 is unsubstituted or substituted phenyl then the ring system



is a piperidine ring; (ii) when W is a substituted or unsubstituted, 5 or 6 membered heteroaryl radical, and A is a $-CH_2CH_2-$ radical and R^1 is hydrogen or lower alkyl, then R^3 is other than lower alkyl.

Most of the above mentioned compounds of formula I(a) are novel and are claimed in U.K. Patent Specification 1,345,872. No examples of oxime derivatives having formula I(a) are given in U.K. Patent Specification No. 1,345,872.

We have now found surprisingly that a small number of oxime derivatives falling within the definition of the formula I(a) above have marked activity as anti-hypertensive agents. Thus this invention provides oxime derivatives having the formula:



(I)

wherein R represents a substituted or unsubstituted phenyl radical; n represents 0 or an integer from 1 to 3 and m represents an integer from 1 to 3 with the proviso that m and n total 3; and the acid addition or quaternary ammonium salts thereof.

Examples of R are unsubstituted phenyl or phenyl substituted by one or more groups, which may be the same or different selected from halogen (for example fluorine, chlorine or bromine), lower alkyl (for example methyl, ethyl, propyl, or butyl), lower alkoxy (for example methoxy, ethoxy, propoxy or butoxy), nitro, amino (including alkyl or dialkyl substituted amino groups) in particular dialkylamino (for example dimethylamino or diethylamino), acylamino in particular alkanoylamino [for example acetylamino (acetamido)], hydroxyl, carboxyl, lower alkoxycarbonyl, alkylenedioxy (for example methylenedioxy), trihaloalkyl (for example trifluoromethyl), mercapto, methylthio, methylsulphonyl and phenyl. Examples of acid addition salts are those formed from inorganic and organic acids in particular pharmaceutically acceptable acid addition salts such as the sulphate, hydrochloride, hydrobromide, hydroiodide, nitrate, phosphate, sulphonate (such as the methane-sulphonate and *p*-toluenesulphonate), acetate, maleate, fumarate, tartrate and formate.

The term "lower" used in relation to alkyl or alkoxy radicals means that the radical contains from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms.

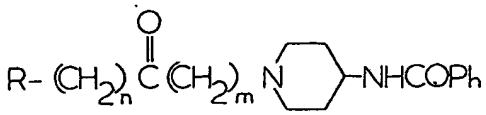
Examples of combinations of values for n and m are 0 and 3 respectively and 2 and 1 respectively. Preferably n is 0 and m is 3.

The compounds of formula I exhibit pharmacological activity, in particular action on the cardiovascular system, especially antihypertensive activity, when tested on warm blooded animals. Compounds of formula I were tested for antihypertensive activity by administering them orally to spontaneously hypertensive rats.

Representative of the antihypertensive compounds of this invention are 4-benzamido-1-(4-hydroxyimino-4-phenylbutyl)piperidine hydrochloride and 4-benzamido-1-(2-hydroxyimino-4-phenylbutyl)piperidine hydrochloride which produced marked decreases (33% and 24% respectively) in blood pressure in the above test at a dose level of 50 m.p.k.

In addition some of the compounds of this invention may be used as intermediates in the preparation of other pharmacologically active compounds as disclosed in our copending Application No. 26099/76, (U.K. Patent Specification No. 1538543). Hence when n is 0 or 1 and m is 2 or 3 the hydroxyimino group may be reduced, for example using a Raney nickel catalyst and sodium hydroxide, to give the corresponding amino substituted analogues, which compounds also possess antihypertensive activity.

A method of preparing the compounds of formula I comprises reacting a compound of formula



(II)

with hydroxylamine. The reaction may be conveniently carried out by heating preferably in the presence of a base, e.g. sodium hydroxide.

As already indicated the compounds provided by the invention contain a basic nitrogen atom and thus can form acid addition salts with acids (particularly pharmaceutically acceptable acids) or quaternary ammonium salts, for example with alkyl halides or aralkyl halides (particularly methyl iodide or benzyl chloride or bromide). The acid addition salts may be formed by treating a free base with the appropriate acid in the presence of a suitable solvent and then the salt isolated. The quaternary

salts may be prepared by treating the free base with the appropriate halide in the presence or absence of a solvent.

The invention also includes pharmaceutical compositions containing as active ingredient an active compound of formula as defined above. The compound may be micronised if desired. In addition to the active ingredient, the compositions also contain a non-toxic carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10—80% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax and cocoa butter. The term "composition" is intended to include the formation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient, with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for istance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances, a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form the composition is sub-divided in unit doses containing appropriate quantities of the active ingredients; the unit dosage form can be a packaged composition, the package containing specific quantities of composition, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 5 mg. or less to 500 or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

The following examples illustrate the invention:

EXAMPLE 1

4-Benzamido-1-(4-hydroxyimino-4-phenylbutyl)piperidine

A solution of hydroxylamine hydrochloride (0.417 g. 0.006 mol) in aqueous sodium hydroxide (2 cm³, 12% w/v) was added to a warm solution of 4-benzamido-1-(4-oxo-4-phenylbutyl)piperidine (1.05 g. 0.003 mol) in ethanol (5 cm³) and heated under reflux for 30 minutes. On cooling the title compound (0.84 g.) separated and was collected by filtration and washed with ethanol. Treatment of the base with ethanolic hydrogen chloride gave the hydrochloride salt, m.p. 217.5°C.

Analysis:

Found:	C, 66.21; H, 7.04; N, 10.12%
$C_{22}H_{27}N_3O_2$. HCl requires:	C, 65.73; H, 7.02; N, 10.45%

EXAMPLE 2

4-Benzamido-1-(2-hydroxyimino-4-phenylbutyl)piperidine

A solution of hydroxylamine hydrochloride (4.5 g. 0.065 mol) in aqueous sodium hydroxide solution (12% w/v, 25 cm³) was added to a warm solution of 4-benz-

amido-1-(4-phenyl-2-oxobutyl)piperidine (11.29 g. 0.032 mol). The solution was allowed to cool and the precipitated solid was filtered and washed with water. The filtrate was treated with a large volume of water and the solid which precipitated was filtered and washed with water. The two solids (8.30 g. 70%) were combined. Two grams of the solid were dissolved in the least amount of ethanol, treated with ethanolic hydrogen chloride, and cooled. The resultin gsolid was filtered off and dried to give 1.25 g. of the hydrochloride of the title compound.

Melting point 192—193°C.

Analysis:

Found:	C, 65.7;	H, 7.20;	N, 10.3%
$C_{22}H_{27}N_3O_2 . HCl$ requires:	C, 65.7;	H, 7.02;	N, 10.4%.

EXAMPLE 3

4-Benzamido-1-[4-(4-hydroxyphenyl)-4-hydroxyimino]piperidine

A solution of hydroxylamine hydrochloride (2.1 g. 0.03 mol) in sodium hydroxide (15 cm³, 12% w/v) was added to a warm solution of 4-benzamido-1-[4-(4-hydroxyphenyl)-4-oxobutyl]piperidine (3.66 grm. 0.01 mol) in ethanol (50 cm³) and the reaction mixture refluxed for 8 hours. The ethanol was evaporated off and the residue treated with water. The solid was filtered off and dried and then recrystallised from ethanol to give a slightly impure title compound (3.4 grm). This was dissolved in the least amount of methanol and treated with ethanolic HCl. Ethyl acetate was added and the solution heated; more ethyl acetate was added to replace the methanol which evaporated. The solution was allowed to cool and the hydrochloride of the title compound filtered off (1.04 gm). Melting point 205—209°C.

Analysis:

Found:	C, 60.31;	H, 6.59;	N, 9.67%
$C_{22}H_{27}N_3O_3 . HCl . H_2O$ requires:	C, 60.33;	H, 6.90;	N, 9.59%.

EXAMPLE 4

4-Benzamido-1-[4-hydroxyimino-4-(*p*-fluorophenyl)butyl]piperidine

Using a procedure analogous to Example 1 4-benzamido-1-[4-oxo-4-(*p*-fluorophenyl)butyl]piperidine may be reacted with hydroxylamine hydrochloride to give the title compound.

EXAMPLE 5

4-Benzamido-1-[4-hydroxyimino-4-(o-methylphenyl)butyl]piperidine

Using a procedure analogous to Example 1 4-benzamido-1-[4-oxo-4-(*o*-methylphenyl)butyl]piperidine may be reacted with hydroxylamine hydrochloride to give the title compound.

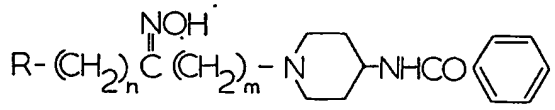
EXAMPLE 6

4-Benzamido-1-[4-hydroxyimino-4-(p-chlorophenyl)butyl]piperidine

Using a procedure analogous to Example 1 4-benzamido-1-[4-(p-chlorophenyl)-butyl]piperidine may be reacted with hydroxylamine hydrochloride to give the title compound.

WHAT WE CLAIM IS:—

1. A compound having the formula



(I)

wherein R represents a substituted or unsubstituted phenyl radical; n represents 0 or an integer from 1 to 3 and m represents an integer of from 1 to 3, with the proviso that m and n total 3; and the acid addition salts and quaternary ammonium salts thereof.

2. A compound as claimed in claim 1 wherein R represents phenyl, or phenyl substituted by one or more groups selected from halogen, lower alkyl, lower alkoxy, nitro, amino, alkanoylamino, hydroxyl, carboxyl, lower alkoxycarbonyl, alkylenedioxy, trihaloalkyl, mercapto, methylthio, methylsulphonyl and phenyl.

3. A compound as claimed in claim 1 or claim 2 wherein n is 0 and m is 3 or n is 2 and m is 1.

4. 4-Benzamido-1-(4-oximino-4-phenylbutyl)piperidine.

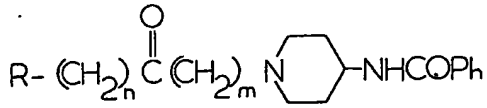
5. 4-Benzamido-1-(2-oximino-4-phenylbutyl)piperidine.

6. 4-Benzamido-1-[4-(4-hydroxyphenyl)-4-oximinobutyl]piperidine.

7. A compound as claimed in any one of claims 1 to 6 when in the form of a pharmaceutically acceptable acid addition salt.

8. A compound as claimed in claim 7 wherein the salt is the sulphate, hydrochloride, hydrobromide, hydroiodide, nitrate, phosphate, methanesulphonate, *p*-toluenesulphonate, acetate, maleate, fumarate tartrate or formate.

9. A process for preparing a compound of formula I as defined in any one of claims 1 to 3 or an acid addition or quaternary ammonium salt thereof which comprises reacting a compound of formula



wherein R, n and m are as defined in any one of claims 1 to 3, with hydroxylamine, and if desired converting the product to an acid addition or quaternary ammonium salt thereof.

10. A process as claimed in claim 9 which is effected in the presence of sodium hydroxide.

11. A process for preparing a compound of formula I substantially as hereinbefore desired with reference to any one of Examples 1, 2 and 3.

12. A compound of formula I whenever prepared by a process as claimed in any one of claims 9 to 11.

13. A pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof in association with a pharmaceutically acceptable carrier.

14. A pharmaceutical composition as claimed in claim 13 when in unit dosage form.

15. A method for preparing a pharmaceutical composition which comprises bringing a compound of formula I or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof into association with a pharmaceutically acceptable carrier.

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